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Serum uromodulin as a marker of kidney graft function*

Uromodulina osoczowa jako marker funkcji nerki przeszczepionej

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Summary

Aim: Serum uromodulin (sURO) was recently found as a sensitive tubular marker in early chronic kidney disease stages. Thus far, mainly early uromodulin urinary excretion was tested in kidney recipients. The aim of our study was to conduct a long-lastinlong-term assessment of sURO in kidney graft function monitoring.

Material/Methods: Forty-one stable kidney recipients (aged 47 (13.7)) were studied around the 3rd month (3m) and the 2nd year (2y) after kidney transplantation. Sera were tested for sURO, creatinine and tacrolimus levels. Kidney biopsy was scored according to revised Banff 97 classification.

Results: sURO level (mean 66.06ng/ml at 3m; 77.81 at 2y) increased borderline significantly (*P = 0.051*) in time and significantly correlated with eGFR (3m RS = 0.46; 2y RS = 0.58), creatinine levels (RS respectively –0.55 and –0.56) and donor age (3m Rs = –0.33; 2y RS = –0.41). We observed borderline correlations between sURO and Banff biopsy scoring: 3m-sURO with arteriolar hyalinosis-ah (RS = –0.3, P = 0.06) and 2y-sURO with peritubular capillaritis-ptc (RS = 0.45, P = 0.07). Correlations of sURO with 3m tacrolimus levels (Rs = 0.3, P = 0.08) were borderline, however patients with CNI toxicity lesions in biopsy had sURO significantly lower (mean 3m-sURO 52.7 vs 83.1 ng/ml; 2y-sURO 61.9 vs 98.1 ng/ml).

Conclusions: sURO can reflect kidney graft quality and function. sURO correlated with ptc, which is considered to be an early marker of a chronic antibody-mediated graft injury. Tacrolimus doesn't influence sURO levels directly, but sURO is lower in patients with toxic kidney injury in biopsy.

Keywords: **calcineurin nephrotoxicity • chronic kidney graft insufficiency • kidney transplantation • ptc-itis • serum uromodulin**

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INTRODUCTION

Uromodulin (URO), known also as Tamm-Horsfall Protein (THP), is a glycoprotein expressed exclusively in the cells of Henle's loop and excreted to the urine [26]. It was found to provide protection against urinary tract infections and stones formation, but also to be involved in kidney innate immunity and water/electrolyte balance regulation [7, 18, 26, 32].

Mutations of URO genes referred to as uromodulinassociated kidney diseases lead to autosomal dominant "ciliopathies": glomerulocystic kidney disease, medullary cystic disease type 2, familial juvenile hyperuricemic nephropathy, all characterized by tubulointerstitial fibrosis, unremarkable urine sediment, hyperuricemia, gout and slow progressive renal failure [4,10]. Other URO gene polymorphisms have also been found to be associated with susceptibility to hypertension by overactivation of the TAL sodium-potassium-chloride cotransporter NKCC2 [19, 30] and to chronic kidney disease (CKD) development and progression [13, 20, 22].

URO was discovered in the urine and so far mainly urinary levels were studied. URO is excreted in the urine at a rate of 50 mg/day, but this amount can be influenced by many factors, including urine volume, diet and exercise [12].

A part of URO enters the bloodstream as a monomer and its blood level is less dependent on external factors. According to the test producer values of URO <100 ng/ml should be suspected for the loss of renal function. In the study of Steubl et al. the mean serum URO (sURO) assayed with ELISA method was 167.6 ng/ml for healthy populations and 111 ng/ml in the first stage of CKD [28]. Dawnay et al. tested serum THP by performing a radioimmunoassay and found it in a range of 70–540 ng/ml in healthy people, undetectable in anephric patients, decreased in hemodialyzed patients, decreased, though in the normal range, in healthy kidney donors and dependent upon initial graft function in kidney transplant recipients. They concluded that THP levels are related to the amount of renal functioning mass [5].

URO was studied as a marker of tubular damage in urine and serum many years ago, but still it has not found usage in clinical practice. Previous studies observed that urinary URO levels are affected by many renal and general medical conditions. They are reduced in diabetic, polycystic, tubulointerstitial nephropathies, lupus nephritis, polycystic ovarian syndrome and elevated in hyperfiltration states (diabetic, pregnancy, uninephrectomy) [32]. Recent research results found sURO to be a better marker of renal function loss, found in persons with interstitial fibrosis or tubular atrophy in CKD, correlating with other established marker as creatinine, estimated glomerular filtration rate (e-GFR) and cystatin C, blood urea nitrogen (BUN) and even more sensitive in early stages of CKD, which solves the problem of undetectable creatinine-blind range of CKD [5, 8, 20, 24, 28]. sURO levels were not affected by age, gender, body mass index, and current smoking status [24]. It is related to tubular secretion rather than glomerular filtration so it reflects a reduction in the number or the function of tubular cells due to loss of kidney tissue and its integrity and represents remaining nephron mass.

There were a few studies about URO in in kidney transplant recipients (KTRs), even while in this group useful markers are especially important. Researchers analyzed mainly urinary URO levels and found it suitable in monitoring the functional state of transplanted kidneys. Urinary URO levels were extremely reduced in delayed onset of graft function and increased after recovery [11]. URO was decreased in urine in acute tubular necrosis, but not in rejection [17]. Other studies have found urinary URO as one of the biomarkers of acute rejection [16]. It increased in acute tubular damage and in 4-14 days prior to clinical symptoms of rejection [25]. It was higher in renal transplant recipients at 6-year transplant follow-up than in matched CKD and controls, associated with worse graft function, outcome, and more severe IFTA in middle tertile levels [23]. The review of Bostom A et al. noticed sURO as a promising biomarker in KTRs and pointed to the need of its validation in large, diverse cohorts of chronic KTRs [2]. The only very recent studies on sURO in KTRs of Steubl et al. found early 1-3 month sURO level comparable to conventional glomerular filtration markers in prediction of graft loss [28] and of Bostom, Steubl et al. who found sURO as a possible indicator of less well-preserved renal tubular function, associated with greater risk for kidney allograft failure in multiethnic cohort of long-term, stable KTRs [1].

The aim of this study was to determine serum URO levels in kidney recipients in relation to GFR, biopsy results, and to immunosuppressive treatment in order to evaluate its usefulness in a long-term graft sufficiency monitoring.

MATERIALS AND METHODS

The study involved 41 stable kidney recipients aged 20-71 (mean 47.37 (13.7), male/female ratio 25:16, transplanted between 2008 and 2011 and monitored up to 2 years. Patients with serious acute conditions, such as acute rejections and serious infectious complications, were excluded from the study.

Clinical data: age, gender, CKD etiology, immunosuppressive treatment (tacrolimus concentrations and steroids doses), immunological parameters (maximal PRA-Panel Reactive Antibodies and HLA – human leukocyte antigens compatibility points) were correlated to sURO levels.

Sera and kidney biopsies were collected twice: at the 3rd month (3m) and at the 2nd year (2y) after the transplantation (only 3 cases were collected at 12 months).

sURO concentrations were assessed with Uromodulin ELISA kit (Euroimmun AG, Lubeck, Germany). Creatinine levels, and proteinuria were determined with standard spectrophotometric techniques (BioMaxima, Poland). GFR (ml/min/1.73m^2) and were estimated according to the MDRD (Modification of Diet in Renal Disease) equation. The concentration was measured with Chemiluminescent microparticle immunoassay (CMIA) using the Architect System (Abbott Laboratories, Abbott Park, IL, USA). HLA was determined with the PCR-SSP method (polymerase chain reaction – sequence specific primers) using HLA Ready Gene DR kit (Inno-train Diagnostic GmbH, Kronberg, Germany) and microlymphocytotoxicity test using HLA Ready Plate ABC kit (Inno-train Diagnostic GmbH, Kronberg, Germany). PRA was determined with microlymphocytotoxicity method.

Kidney biopsy was assessed according to the revised Banff 97 classifications [27]. Histopathological grading for interstitial fibrosis (ci), tubular atrophy (ct), fibrous intimal thickening (cv), and arteriolar hyalinosis (ah), arteritis (v), tubulitis (t), peritubular capillaritis (ptc), mesangial matrix increase (mm), allograft glomerulopathy (cg), mononuclear cell intestinal inflammation (i), based on the criteria suggested by the Banff scoring system was correlated with sURO.

The study protocol was approved by the institutional Bioethics Committee (decision BN-001/2/08). Informed consent was acquired from each patient.

Results were analyzed with Statistica 7.0 software. Since distributions of most biochemical parameters were significantly different from normal distribution ($p < 0.05$, Shapiro-Wilk test), the following non-parametric tests were used for statistical analysis of quantitative variables: the Kruskal-Wallis one-way analysis of variance (KW) and the Mann-Whitney U tests (MWU) were used in data comparisons, Wilcoxon signed-rank test to assess the significance of changes between the two time points. Spearman range (SR) test was used in correlation testing and expressed as a RS coefficient. Two-tailed values of $P < 0.05$ were considered statistically significant.

RESULTS

sURO was tested in all 41 patients twice and its levels ranged from 11.38 to 200.78 (mean 66.06 (42.26)) ng/ml at 3m and 12.51–202.78 (mean 77.81 (49.57)) at 2y. The increase in sURO levels between the two time points was on the border of statistical significance (Wilcoxon signed-rank test, *P = 0.051*). Only 14.6% of 3m and 21.9% of 2y sera were above 100 ng/ml. Mean values of other tested parameters (GFR, creatinine, creatinine increases from minimal posttransplant level, proteinuria, prednisone dose, tacrolimus concentration) at 3m and 2y and their correlations with sURO levels are shown in Table 1. sURO levels significantly correlated with eGFR, creatinine levels, and creatinine increases from minimal posttransplant level in both 3m and 2y sera (Table 1).

Urine protein concentrations did not correlate significantly with sURO levels. Borderline significant correlations were found between sURO and immunosuppressive treatment: positive with tacrolimus levels at 3m and negative with steroid doses at 2y.

There was a significant difference in 3m and 2y sURO levels between groups with and without calcineurin toxicity (CNI) features in some biopsies done during the observation period (mean 3m sURO 52.7 ng/ml in 23 CNI positive vs 83.1 ng/ml in 12 CNI negative, *P = 0.04* ; mean 2y sURO 61.9 ng/ml vs 98.1ng/ml, *P = 0.02*).

IFTA/CAN (intestinal fibrosis and tubular atrophy/chronic allograft nephropathy) features were observed in 5.1% (2 of 39) of 3m biopsies and in 21.1% (4 of 19) of 2y biopsies. sURO levels were higher in patients with IFTA/CAN features some any biopsy, but due to low numbers the differences were not significant (means at 3m 64.82 ng/ml for 12 IFTA/CAN positive vs 66.58 ng/ml for 29 IFTA/CAN negative patients *P = 0.7* ; at 2 y 67.01 ng/ml vs 82.28 ng/ml; *P = 0.25*).

Correlations between sURO levels and biopsy results scoring were on the border of significance: 3m sURO correlated with ah (RS = –0.31; P = 0.06; mean sURO level 76.7 ng/ml at 23 patients without ah features in 3m biopsy results vs 50.4 in 15 patients with ah features *P = 0.06*), 2y sURO correlated with ptc (RS = 0.45; P = 0.07 ; mean sURO level 148.8ng/ml in 2 ptc positive patients vs 71.6 ng/ml in 16 patients without ptc, *P = 0.09*). There were no ptc positive biopsies at 3m, and for both 2y ptc positive patients sURO level increased on average by 75.4 ng/ml at the time of observation.

Table 1. Correlation of serum uromodulin (sURO) with other markers of kidney function and drug levels

Parameter	n	Mean (SD)	Correlation with sURO	
			RS	P – value
3m eGFR, ml/min/1.73m^2	38	53.1 (22.5)	0.46	0.004
3m creatinine concentration, mg/dl	38	1.56 (0.64)	-0.55	<0.001
3m creatinine increase [a], mg/dl	38	0.44 (0.44)	-0.40	0.01
3m proteinuria, mg/dl	39	16.67 (50.9)	0.12	0.45
3m tacrolimus concentration, ng/ml	35	12.81 (3.52)	0.30	0.08
3m prednisone doses, mg	41	13 (6.4)	-0.03	0.84
2y eGFR, ml/min/1.73m^2	36	62.7 (21.8)	0.58	<0.001
2y creatinine concentration, mg/dl	36	1.4 (0.77)	-0.56	<0.001
2y creatinine increase [a], mg/dl	36	0.24 (0.48)	-0.30	0.07
2y proteinuria, mg/dl	34	8.53 (19.2)	-0.28	0.10
2y tacrolimus concentration, ng/ml	31	7.4 (2.4)	-0.09	0.64
2y prednisone doses, mg	29	4.3 (2.4)	-0.35	0.06

3m - 3 months after the transplantation, 2y – 2 years after the transplantation,
eGFR – estimated glomerular filtration rate, n – number, RS – Spearman correlation coefficient, SD – standard deviation, sURO – serum uromodulin concentration,
[a] – creatinine increase from minimal posttransplant level

sURO concentrations in both 3m and 2y sera significantly negatively correlated with kidneys donor age (3m Rs = –0.33, P = 0.04; 2y RS = –0.41.6, P = 0.007).

We did not notice significant correlations of sURO levels with immunological parameters (HLA compatibility points), and compatibility points and PRA percentages, and differences of sURO levels between patients of different gender, kidney insufficiency etiology and blood groups.

DISCUSSION

Facing kidney donors shortage, transplant nephrologist are still looking for useful markers for kidney graft function monitoring. The most popular markers used worldwide in clinical practice today are serum creatinine and creatinine-based GFR equations (eGFR), which reflect mainly glomerular function. The usefulness of other markers such as NGAL, cystatin c in kidney transplant patients is being studied.

Serum uromodulin (sURO) was recently described as a good marker of kidney function monitored in patients with CKD [20, 24, 28]. Reduced serum concentrations of uromodulin were found in persons with interstitial fibrosis or tubular atrophy in the course of chronic kidney disease and it was found as useful marker for a number of remaining functional nephrons secretion [28]. sURO is related more to tubular cells function, which is why other functions than those reflected by GFR, and can adequately represent the remaining kidney tissue mass [5]. It is also independent from external factors [24]. There are not many studies about URO in transplant patients, even while in this group useful markers are especially important. Most of them estimate mainly the glomerular function, while chronic rejection process takes place mainly in kidney intestine and also leads to interstitial fibrosis or tubular atrophy. In kidney recipients, uromodulin urinary excretion was so far mainly tested and only the recent studies of Steubl and Bostom at al. on transplant patients found early 1–3month sURO levels comparable to conventional glomerular filtration markers in prediction of graft loss [29] and lower sURO as possible indicator of less well-preserved renal tubular function, associated with a greater risk for kidney allograft failure in long-term stable KTRs [1].

Due to the mentioned sURO advantages, our goal was to study its long lasting usefulness in stable kidney recipients monitoring in comparison to eGFR and relation to biopsy results. We have decided to test patients with no acute complications for over 2 years after a transplantation to find sURO sensitivity in reflecting kidney mass and early function loss. To our knowledge, we are the first study to test sURO in serum of stable kidney graft recipients in time.

We have found significant correlations of sURO with creatinine and GFR at the 3rd month and at the 2nd year of observation, which can suggest that sURO can be considered as a useful marker of kidney function. For transplant patients a reduction of URO urinary excretion was observed in delayed graft function [11], acute tubular necrosis [17], and an increase was observed in acute tubular damage and rejection [16]. Reznichenko tested urinary levels of URO in renal recipients between 2.5-12 years after a transplantation and found them to be elevated in recipients compared to healthy and CKD patients, and associated with a worse prognosis [23].

The manufacturer of the URO ELISA test and Steubl et al. suggested sURO level of below 100 ng/ml as indicative of the patient's kidney insufficiency [28]. According to our study, sURO concentrations in patients after a kidney transplantation in the majority are below 100 ng/ml (14.6% 3m and 21.9% 2y were above 100 ng/ml), so most kidney recipients should be interpreted as kidney insufficient patients. These results are in agreement with GFR values, where mean GFR was 53 ml/min/1.73m^2 at 3m and 62 ml/min/1.73m^2 at 2y, so also below normal ranges. Thus, kidney recipients require different criteria by which to interpret sURO levels than non-transplant patients; however, sURO can still be useful in monitoring kidney function. We have chosen the 3rd month as the time when a kidney should take up its function and recover after an unstable post-transplant period and before it is destroyed by post-transplant complications. Since the manufacturer recommends sURO as a sensitive marker in early stages of CKD, we tested sURO levels at 2 years after a transplantation and compared them with eGFR, creatinine, and biopsy results. According to Uslu et al. creatinine, estimated GFR, cystatin C remained stable in the first year despite the sum of interstitial fibrosis and tubular atrophy score increase found in protocol biopsies [32]. sURO levels were not significantly lower in patients with IFTA/CAN features due to the low IFTA/CAN positive biopsy numbers. sURO levels correlated negatively at 3m with the ah score (arteriolar hyalinosis) and positively at 2y with the ptc score (peritubular capillaritis). Arteriolar hyalinosis is a symptom of a chronic kidney injury, regarded as irreversible. It has been associated with aging, vascular diseases, diabetes and hypertension. In transplant patients it is observed in kidneys of older donors and as a marker of CNI nephrotoxicity, prognosing a worse graft survival [3, 6]. Thus, lower sURO levels in patients with higher ah score in biopsy may reflect the condition of a graft, which is confirmed by its correlation with the donor's age.

Peritubular capillaritis is a marker of active inflammatory changes in a kidney. Recent studies suggest ptc-itis as an early detection marker for patients at risk of a chronic antibody mediated rejection, which correlates independently with the graft function and outcome [9, 14, 15, 21]. We did not observe ptc-its at 3m biopsies and patients with ptc-itis at 2y biopsy had a much higher level of sURO, which increased by 75 ng/ml during observation. It is possible that a release of sURO to the serum, which is an immunologically active protein, was stimulated during active inflammation and an increase in sURO levels can be a sensitive marker of early stages of chronic graft rejection.

Despite URO being the most abundant protein secreted in urine, we did not find any correlation of sURO with protein concentration in urine. Urine exertion is much more dependent on external factors such as urine volume, a person's diet, and exercise [12].

According to our observations, sURO level is more dependent on the condition of the transplanted kidney. It negatively correlates with the donor's age, especially at 2y. Also, the negative correlations of sURO with ah Banff scoring can be related to the previous graft's condition. This confirms that it is a sensitive marker of kidney tissue mass loss. The same relation to age was observed in the healthy population and in patients with first stages of CKD [24]. sURO levels were not related to immunological conditions such as tissue compatibility or immunisation degree (HLA and PRA), but they did correlate with immunosuppressive drugs regiment. The correlations of sURO with tacrolimus concentrations at 3m and with steroid doses in 2y were borderline. Better graft function at 2y probably requires lower steroid doses. Surprisingly, the correlation with tacrolimus levels at 3m was positive (borderline significance) with no correlation found at 2y. However, sURO levels were lower in patients with CNI toxicity features in biopsy results, suggesting that toxic damage in kidneys decrease URO levels. There is currently no information from other studies on immunosuppressive drug influence on sURO levels that could explain our observations. It may indicate that tacrolimus does not influence sURO directly and that a stronger immunosuppressive treatment in the initial months protects kidneys tubules from inflammatory damage, or that tacrolimus toxicity may at the beginning induce an increased uromodulin release, which is a protective protein. sURO seems to be a promising marker of kidney graft function; however, more studies on larger groups are needed to evaluate its usefulness.

CONCLUSIONS

sURO correlated with GFR and donor's age, which is why sURO can reflect kidney graft quality and function. It seems that tacrolimus does not influence sURO levels directly, but a toxic kidney injury confirmed by biopsy, leads to sURO decrease. sURO positively correlated with ptc, which is considered to be an early marker of a chronic antibody-mediated graft injury. sURO seems to be a promising marker in kidney graft function monitoring; however, its usefulness requires more and larger studies.

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